

# **Developing Risk Reduction Strategies through Metabolic Profiling**

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- 1) Risk reduction strategies: prevention, intervention and treatment.**
- 2) Strategies are designed based on information: knowledge of genome and its expression, knowledge of proteins and their structural and spatial relationships, and knowledge of metabolic functions.**

# Biochemical Reaction



$$\vec{V}_0 = \frac{\vec{V} S_0}{S_0 + K_m}$$

Dependence on substrate and  
genomic/proteomic variables

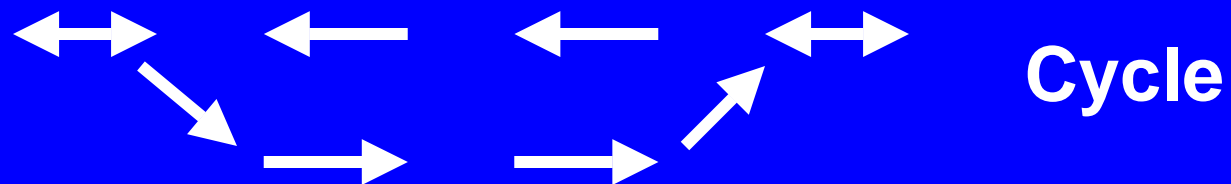
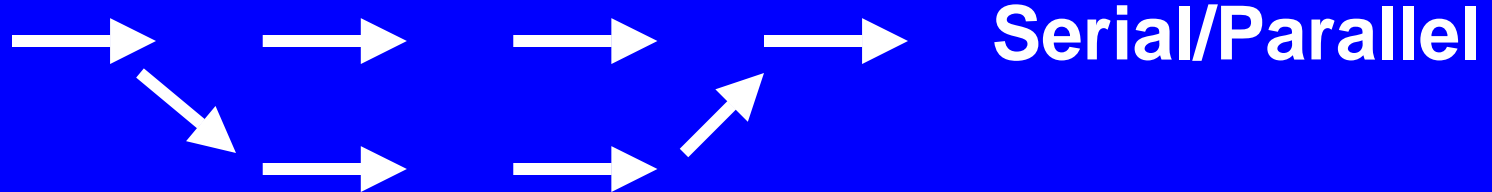
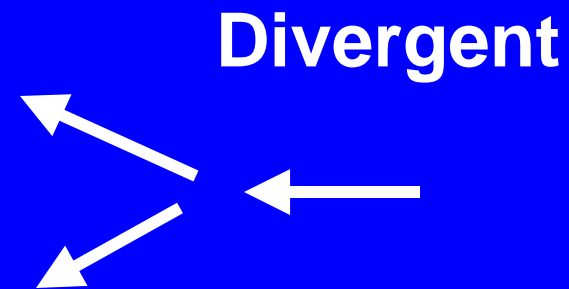
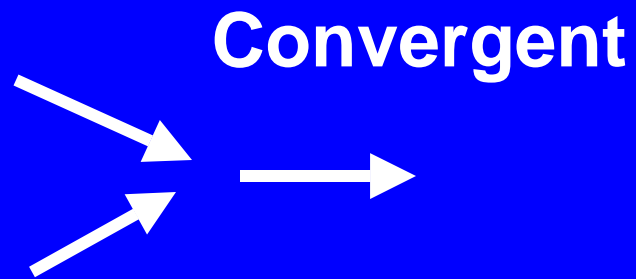
# Linear Pathways

Linear unidirectional pathway

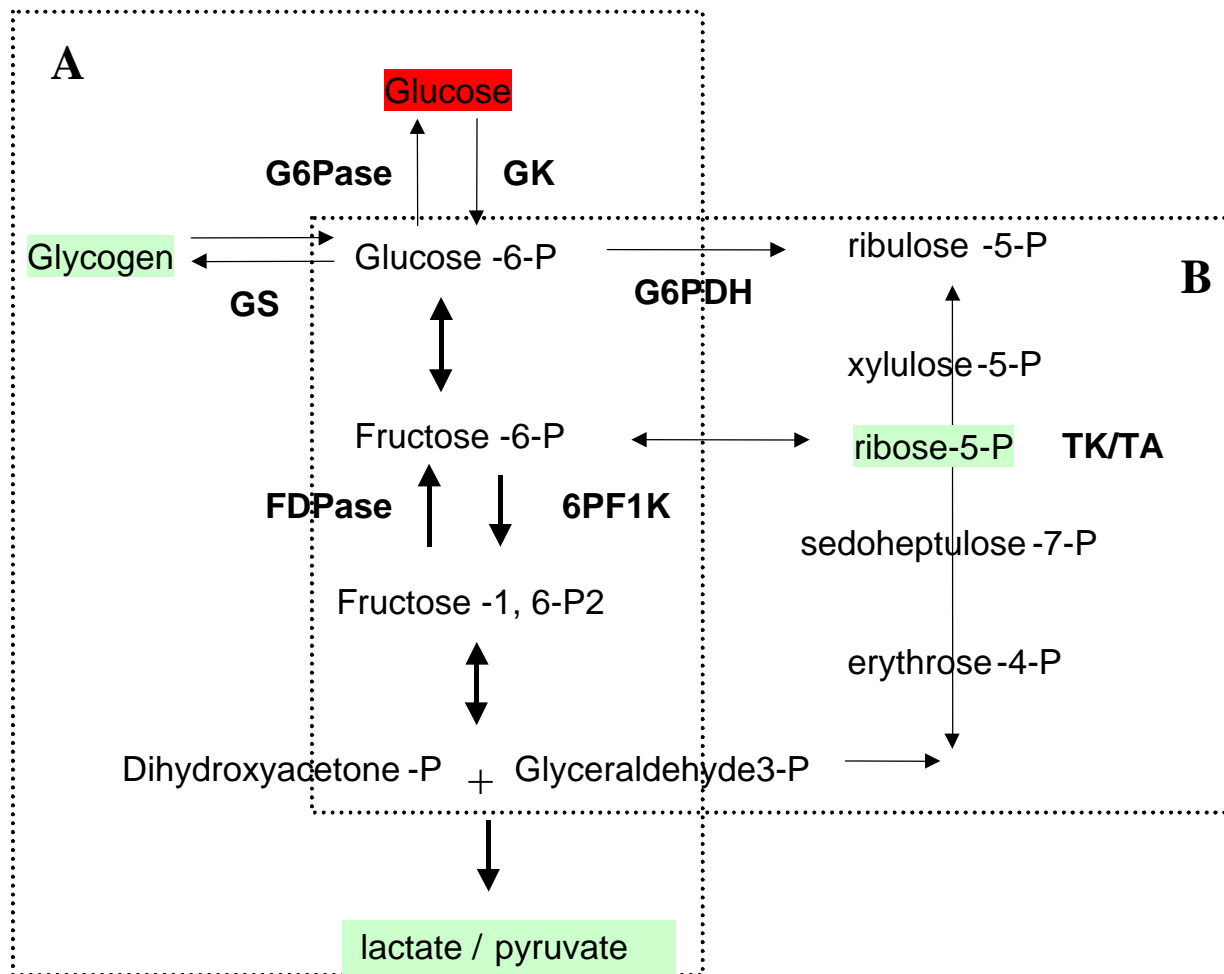


Genomics, proteomics and  
metabolomics give  
equivalent information.

# Organization of Pathways



# Example of Metabolic Network



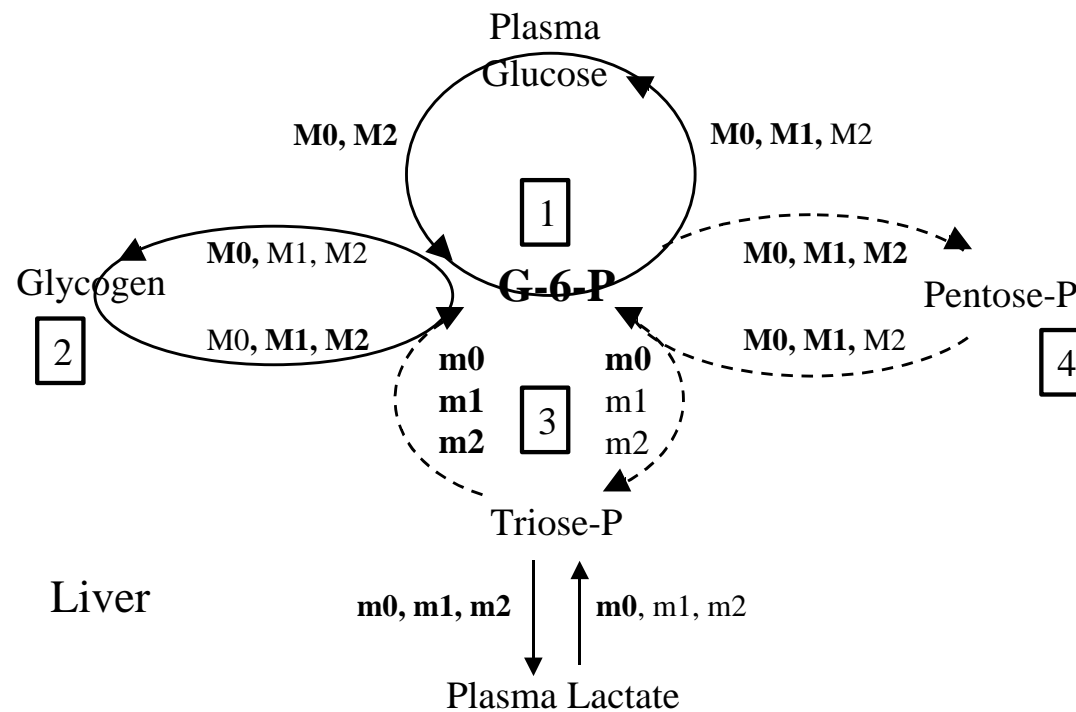
- 1) Perturbation the glucose metabolic network affects both the forward and reverse reactions of these substrate cycles.**
- 2) The response to precursor is specific resulting in a change of direction and magnitude of redistribution of metabolic intermediates.**
- 3) The interconnection of these cycles allows optimal distribution of substrate throughout the network.**

**Metabolic function of a living system can be characterized by the distribution of substrates, the direction of net fluxes and changes in substrate cycles.**

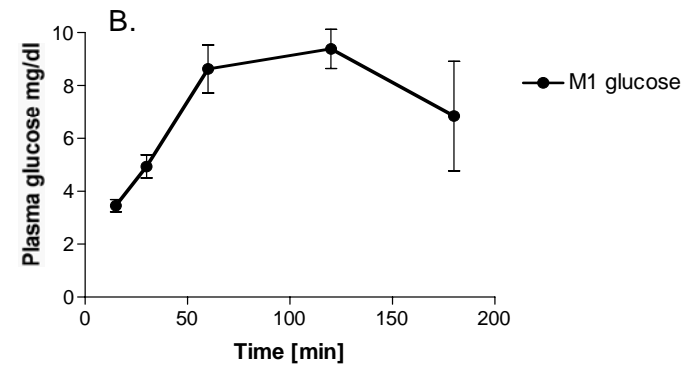
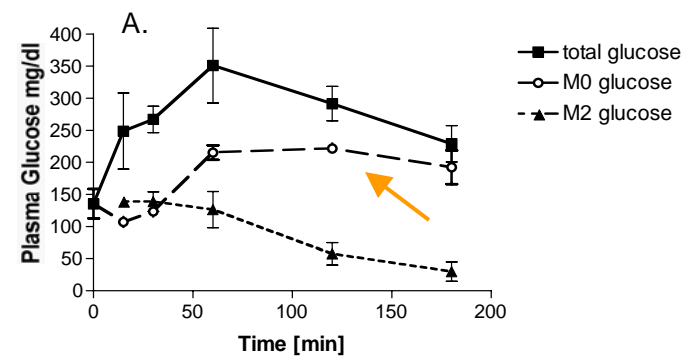
**Metabolic Profiling can be achieved with the use of appropriate stable isotope tracers and mass spectrometry (GC/MS or LC/MS).**

**The study of substrate cycles in hepatocytes is a powerful tool for the screening of drugs which may affect hormone signaling pathways as related to hepatic glucose metabolism in diabetes.**

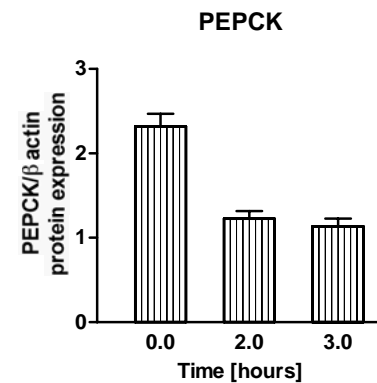
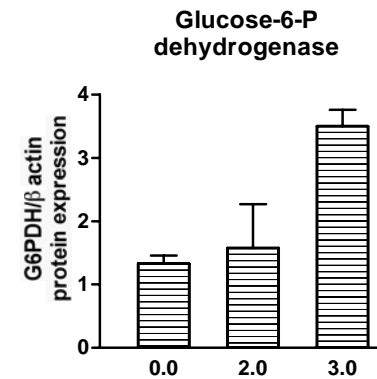
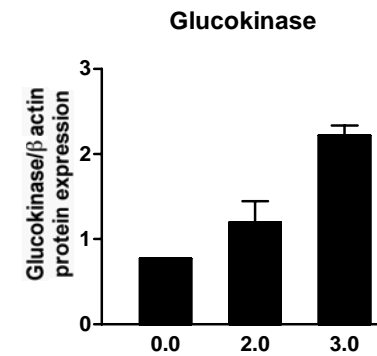
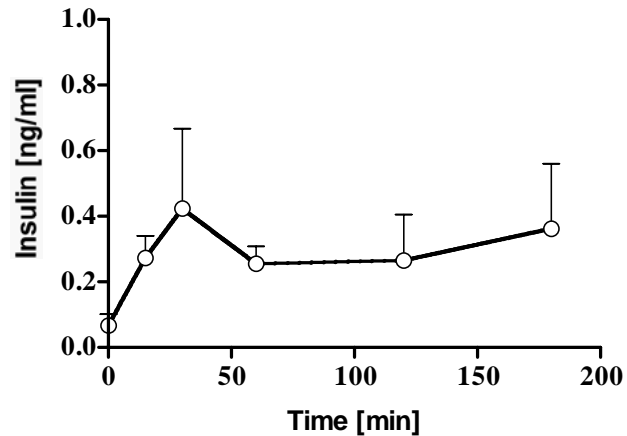
# Substrate Cycles during IPGTT



# Glucose Isotopomers during IPGTT

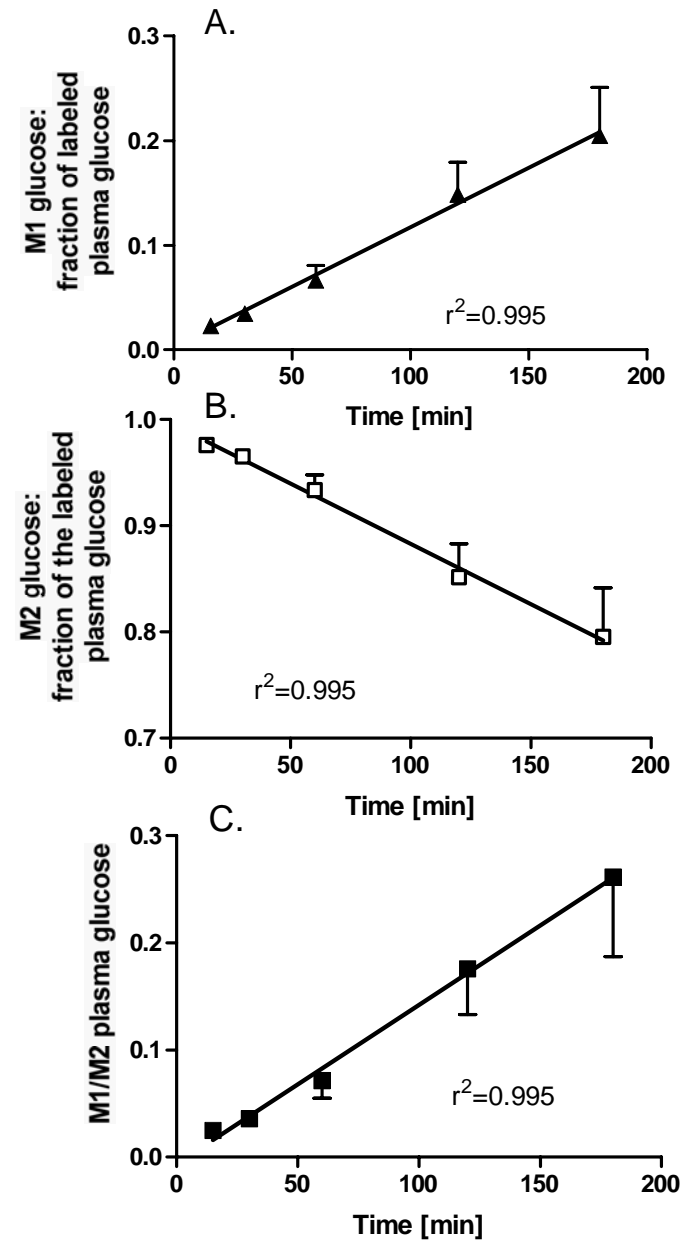


# Time Course of Plasma Insulin and Molecular events



**Recycling is  
glucose  
dependent.**

$$\frac{d(M1/M2)}{dt} = \frac{dM1}{(M2)dt} - \frac{M1}{M2(M2)} \frac{dM2}{dt}$$



**Concentration dependent nature of glucose recycling cannot be derived from genomic or proteomic information alone. Therefore, metabolic information is absolutely necessary in order to have a better understanding of biological behavior.**

**The induction of expressions and subsequent modification of enzymes by hormones are modulated by substrate cycles of the glucose metabolic network.**

**Futile cycling minimizes the impact of acute changes in substrate concentration during IPGTT.**

**G6Pase/GK futile cycle is associated with insulin resistance in diseases like Cushing's syndrome and diabetes.**

# **Implications of Metabolic Network on Risk Reduction Strategies**

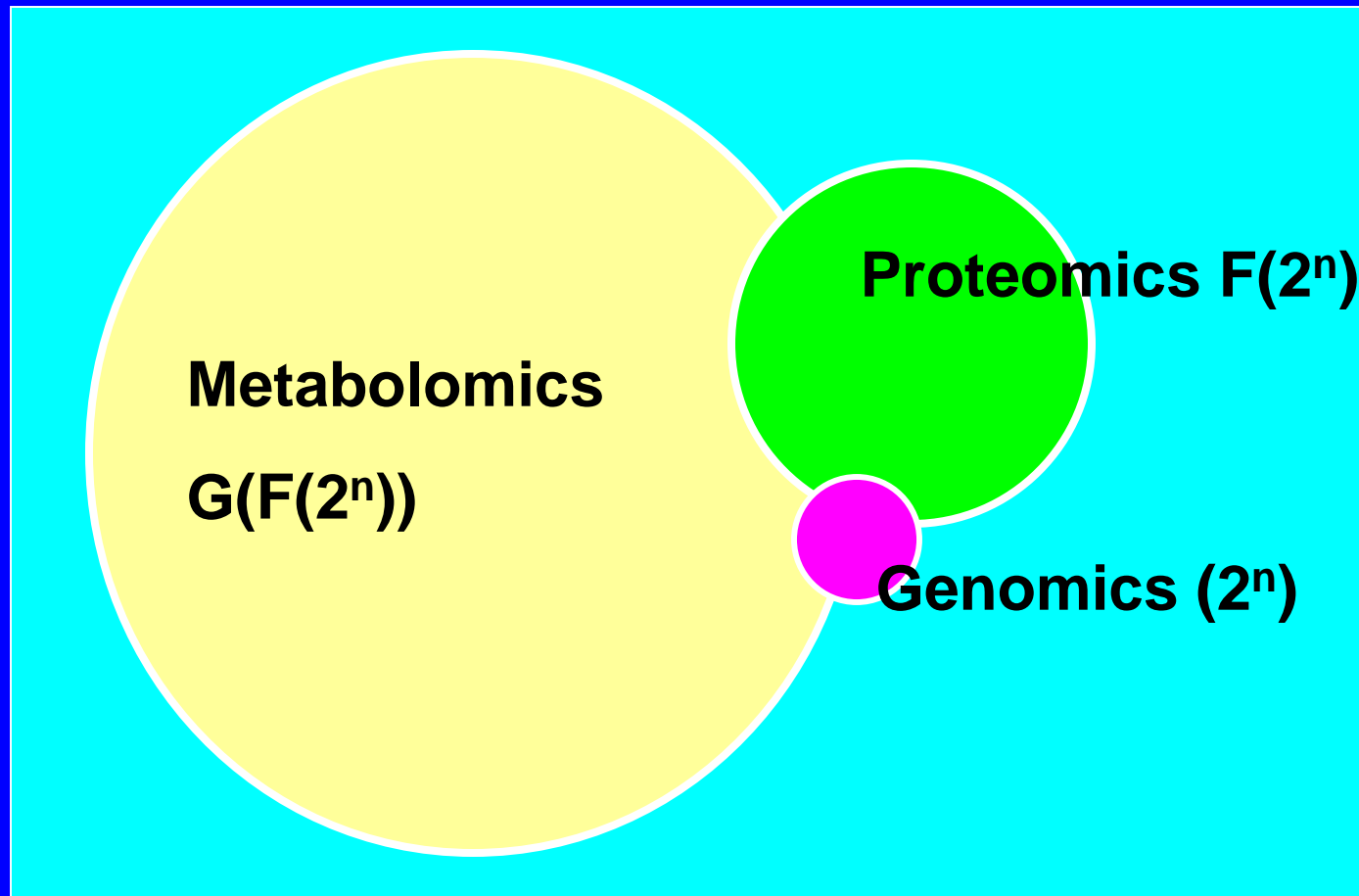
- 1) Each intervention or treatment will have multiple endpoints.**
- 2) Conventional dose-response curves are usually not applicable.**
- 3) Dynamic assessment is required.**
- 4) Environmental context (substrate environment) is important.**

**Metabolic Profiling is the dynamic assessment of redistribution of substrates for a particular state of genetic expressions and substrate environment.**

**Metabolic Profiling allows the determination of various metabolic end-points of the metabolic network. Dose-response curve for each metabolic end-point can be constructed.**

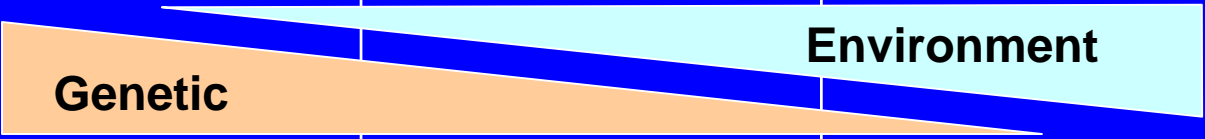
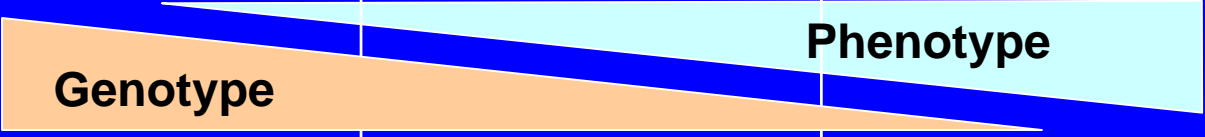
**Risk Reduction Strategies can be developed to optimize between the attainment of desirable end-points and the avoidance of undesirable end-points.**

# Relative Bio-Informatic Units



**Universe of Bio-Informatics**

# Conceptual Considerations of Bio-Informatics Disciplines

	Genomics	Proteomics	Metabolic Profiling
Mechanism			
Genotype / phenotype			
Dynamic vs Static	Static (scalar)	Static (scalar)	Dynamic (vector)
Comparison with language	Words (dictionary)	Grammar (rules)	Story

# Practical Considerations of Bio-Informatics Disciplines

	Genomics	Proteomics	Metabolic Profiling
Data acquisition	<u>Multiplexing</u> and parallel processes	Multiplexing and parallel processes	Multiplexing and <u>parallel processes</u>
Data Analysis	Pattern recognition	Structural models	Metabolic models
Data Storage and retrieval	Search by genes	Search by proteins	Search by metabolic function

# Conclusion

**Metabolic Profiling is essential to the development of risk reduction strategies. Metabolic Profiling provides a metabolic mechanism for drug action or toxicity, and an understanding of dose response relationship for potential therapeutic benefits and untoward reactions.**

# Acknowledgement

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